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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/026,276	02/19/98	KENTEN J	IGN-9601

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EXAMINER	
HAMUD,F	
ART UNIT	**PAPER NUMBER**
1647	17

DATE MAILED: 08/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File copy

Office Action Summary

Application No.	Applicant(s)
09/026,276	KENTEN et al
Examiner	**Group Art Unit**
Fozia Hamud	1647

☒ Responsive to communication(s) filed on *May 30, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *2-8, 14-19, 21-27, 33-36, 38-40, 42-47, 51-57, 59-63, 70-75, and 81-83* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *2-8, 14-19, 21-27, 33-36, 38-40, 42-47, 51-57, 59-63, 70-75, and 81-83* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 2, 4, 8, 21, 42, 59 and 81 have been amended in Paper No.16, filed on 5/30/2000. Thus claims 2-8, 13-27, 33-47, 53-64, 70-75 and 81-83 are pending and under consideration by the Examiner.

2. Receipt of Applicant's arguments and amendments filed in Paper No.16, 5/30/00 is acknowledged.

3. The following previous rejections and objections are withdrawn in light of Applicants amendments filed in Paper No.16, 5/30/00:

(I) The rejection of claims 2-8, 13-19, 21-27, 33-36, 38-40, 42-47, 53-56, 59-64, 71-75 and 81-83 made under 35 U.S.C. §112, second paragraph.

(ii) The rejection of 42-43, 53, 70, 74 made under 35 U.S.C *§ 102*(e) as being anticipated by Rechsteiner et al (US Patent 5,763,225).

(iii) The rejection of 42-43, 53, 70, 74 made under 35 U.S.C *§ 102*(e) as being anticipated by Wittliff et al (1990).

(iv) The rejection of claims 42-43, 53, 70, 74, made under 35 U.S.C *§ 102*(b) as being anticipated by Vannier et al (1996).

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Applicant's arguments filed in Paper No.16, filed on 5/30/00, have been fully considered and were deemed persuasive in part. The issues remaining as well as new issues, are restated below.

Claim rejections-35 USC § 102

6a. Claims 2-3, 8, 13, 21, 22, 27,33, stand rejected under 35 U.S.C *§ 102*(e) as being anticipated by Rechsteiner et al (US Patent 5,763,225), for reasons of record set forth in pages 4-5, in Paper No:14, mailed on January 24, 2000.

With respect to claims 2-3, 8, 13, 21, 22, 27, 33, 42-43, 53, 70, 74-75 Applicants argue that this rejection has been obviated by the amendment of claim 2 to include the limitation that the epitope containing segment is not efficiently cleaved from the ubiquitin fusion protein by exposure to ubiquitin-specific proteases in vivo. Applicants contend that the ubiquitin fusion protein disclosed by Rechsteiner et al is intended to have a C-terminal extension which is susceptible to cleavage by ubiquitin specific proteases, and that modifications to make the ubiquitin-fusion protein non-cleavable are not discussed in the disclosure. With respect to claims 27, Applicants argue that the Rechsteiner et al reference does not disclose ubiquitin fused to two or more non-contiguous epitope-containing segments, and that non-contiguous indicates that the epitope-containing segments are located at different sites of the ubiquitin protein. With respect to claims 42-43 and 53, Applicants also argue that Rechsteiner et al do not teach a ubiquitin fusion protein having fusion s located at the N-terminus or an internal site of the ubiquitin protein.

These arguments were fully considered but are deemed unpersuasive. Rechsteiner et al reference still anticipates amended claims 2, 21 and 42. Rechsteiner et al disclose synthesis and recovery of ubiquitin-carboxyl extension peptides wherein the peptides contain two to forty amino acid residues, and wherein the peptides can be recovered as ubiquitin fused extension products (Ub-CTEP) or alternatively can be cleaved from the ubiquitin by an appropriate peptidase, (abstract, column 2, lines 53-55). Thus the alternative embodiment where the peptide is recovered still fused to ubiquitin,

anticipates amended claims 2-3, 8, 13 and 75. With respect to claims 21, 22, 27 and 33, the ubiquitin-fusion protein disclosed by Rechsteiner et al comprises ubiquitin fused to peptides of about 40 amino acid residues and immunizing an animal with said ubiquitin-fusion protein would result in the generation of anti-peptide antibodies. It is inherent that the 40 amino acid residue peptide to be fused with ubiquitin to contain epitopes at the N-terminus and C-terminus, thus the ubiquitin fusion protein comprises a non-contiguous epitope containing segment. With respect to the argument that "non-contiguous" indicates that the epitopes are attached to different sites of the ubiquitin protein, the claim does not recite that "the epitopes" should be attached to different sites of the ubiqiuitin, therefore, Applicant is arguing limitations that are not in the claims.

6b. The rejection of claims 2-3, 8, 13, 21, 22, 27, 33 and 75, made under 35 U.S.C *§ 102*(e) as being anticipated by Wittliff et al (1990) is maintained for reasons of record set forth in the office mailed on January 24, 2000, page 6 in Paper No:14.

Applicants argue that Wittliff et al teach the expression and characterization of an active human estrogen receptor as a ubiquitin fusion protein, however, Wittliff et al do not disclose ubiquitin fused to two or more identical epitopes, therefore, it does not anticipate claims 2-3, 8 and 13. Applicants also argue that since Wittliff does not teach a fusion protein with non-contiguous epitopes it does not anticipate claim 27, and that non-contiguous indicates that the epitope-containing segments are located at different sites of the ubiquitin protein.

These argument are not persuasive, because the hFSHR inherently comprises more than one epitope, some of which are not contiguous. With respect to "non-contiguous" epitopes, as indicating

epitopes that are attached to different sites of ubiquitin, the claims do not recite a limitation where epitopes are attached to different sites of ubiquitin.

6c. The rejection of claims 2-3, 8, 13, 21, 22, 27, 33 and 75, made under 35 U.S.C *§ 102*(e) as being anticipated by Vannier et al (1996) is maintained for reasons of record set forth in the office mailed on January 24, 2000, pages 6-7, in Paper No:14.

Applicants argue that Vannier et al teach a fusion protein comprised of ubiquitin fused to the extracellular domain of amino acid 23-358 of human FSH receptor to the C-terminus of ubiquitin, thus this fusion protein does not contain two or more identical epitopes or tow or more non contiguous epitopes.

This argument is not persuasive, because the hFSHR inherently comprises more than one epitope, and some of these epitopes are not contiguous.

Claim rejections-35 USC § 103

7a. The rejection of claims 15, 35, 55, 72, 81 and 83 made under 35 U.S.C. 103(a), as being unpatentable over Van der zee et al in view of Vannier et al, is maintained for reasons of record set forth in pages 10-12, in Paper No:8, mailed on April 26,1999 and reiterated in pages 3-4 of the office action mailed on 01/24/00.

Applicants argue that the ubiquitin fusion protein of the present invention provides the double advantage of conferring antigenicity to a relatively small peptide sequence, which allows specific targeting of the immunogenic response to one or two epitopes of a protein and generating minimal if any immune response to the ubiquitin carrier, and that large peptides/proteins are often immunogenic in the absence of a carrier, while small peptides are not. Applicants also argue that the

ability of ubiquitin to function well as a carrier for the epitopes specified by the applicant's invention could not have been predicted by one of skill in the art with any degree of certainty, because ubiquitin is highly conserved protein and thus is minimally antigenic itself.

With respect to Applicants first argument, Applicants are arguing limitations that are not in the claims. The size of the peptide fused to ubiquitin is irrelevant to the instant claims. Also since Vannier et al was able to elicit an immune response against FSHR fused to ubiquitin, it would be obvious to the skilled artisan to fuse small peptides to ubiquitin with great expectation of success to elicit an immune response against said small peptides, because there is nothing in the Vannier et al reference that suggests that small peptides fused to ubiquitin may not elicit an immune response.

With respect to Applicants second argument, Vannier et al was able to elicit an immune response against the Ub-FSHR protein, showing that ubiquitin functions well as a carrier, therefore, it would be obvious to the skilled artisan to fuse ubiquitin to the epitopes specified by Applicants to induce an immune response against said epitopes, with great expectation of success.

7b. Claims 4-7, 14-19, 21-26, 33-36, 38-40, 44-47, 54-56, 59-64, 71-73 and 81-83 stand rejected under U.S.C. § 103 as being unpatentable over Wittliff et al in view of Van der Zee et al (1995).

Applicants argue that Wittliff et al teach a ubiquitin fusion protein, wherein the complete amino acid sequence of the human estrogen receptor is fused to the C-terminus if ubiquitin and that the fused protein is expected to be antigenic in the absence of a carrier.

This argument is not persuasive, because Wittliff et al demonstrated that the UB-ER fusion behaved identically as the wild type receptor and is recognized by monclonal antibodies against two

epitopes of the human estrogen receptor, thus showing that ubiquitin functioned well as carrier and that an immune response was not elicited against it.

Claim rejections-35 USC § 112, second paragraph

8a. Claims 2-8, 14-19, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8b. Claim 2, recites ".....wherein the epitope containing segment is not efficiently cleaved from the ubiquitin fusion protein by exposure to ubiquitin-specific proteases in vivo....", however, it is unclear what Applicants mean by "...efficiently cleaved..", does it mean that the epitope containing segment is cleaved 10% of the times, 90% of the times, or 100% of the times? Appropriate correction is required.

Claims 3-8 and 14-19 are vague and indefinite so long as they depend on claim 2, for the limitation set forth directly above.

Conclusion

9. No claim is allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit1647
August 14, 2000

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